THE CLAIMS:

1. A method for selecting compositions having potent ability to increase the permeability of a body surface as candidates for further testing for low irritation potential, comprising the following steps:

(a) providing a library, said library comprising a plurality of samples, each sample comprising at least two chemical penetration enhancers;

(b) measuring with a high throughput device the abilities of the samples to increase the permeability of a test membrane; and

(c) analyzing the measurements to select compositions having potent ability to increase the permeability of said body surface.

2. The method of claim 1 in which the abilities of the samples to increase the permeability of the test membrane are measured by a method comprising:

(a) securing the test membrane to a device comprising a donor plate, the donor plate including a plurality of donor holes passing through the donor plate;

(b) introducing the samples into donor holes, each sample including a test substance; and

(c) evaluating the amount of the test substance that remains in the donor holes or that migrates into the test membrane after a suitable incubation time.

3. The method of claim 1 in which the abilities of the samples to increase the permeability of the test membrane are measured by a method comprising:

(a) securing the test membrane to a device comprising a donor plate, the donor plate including a plurality donor holes passing through the donor plate;

(b) securing the test membrane to a receiver plate such that the test membrane is disposed between the donor plate and the receiver plate, said receiver plate including a plurality of receiver wells corresponding to the donor holes and said receiver wells containing a liquid;

(c) introducing the samples into donor holes, each sample including a test substance; and

(d) evaluating the amount of the test substance in each donor hole that

migrates through the test membrane into the receiver well corresponding to said donor hole.

4. The method of claim 1 wherein the test membrane is mammalian skin or mucosa.

5. The method of claim 1 wherein the abilities of the samples to increase the permeability of the test membrane are measured by making a plurality of electrical conductivity measurements.

6. The method of claim 1 in which each of a plurality of the samples comprises three chemical penetration enhancers.

7. The method of claim 1 in which each of a plurality of the samples comprises four chemical penetration enhancers.

8. The method of claim 1 in which each of a plurality of the samples comprises more than four chemical penetration enhancers.

9. The method of claim 1 in which the library contains more than 1,000 samples.

10. The method of claim 1 in which the library contains more than 10,000 samples.

11. The method of claim 1 in which the library contains more than 1,000,000 samples.

12. The method of claim 1 in which the library contains more than 10,000,000 samples.

13. The method of claim 1 in which one or more of the chemical penetration enhancers are selected from the group consisting of N-Acyl-hexahydro-2-oxo-1H-azepines, N-Alkyl-dihydro-1,4-oxazepine-5,7-diones, N-Alkylmorpholine-2,3-diones, N-Alkylmorpholine-3,5-diones, Azacycloalkane derivatives (-ketone, -thione), Azacycloalkenone derivatives, 1-[2-(Decylthio)ethyl]azacyclopentan-2-one (HPE-101), N-(2,2), Dihydroxyethyl) dodecylamine, 1-Dodecanoylhexahydro-1-H-azepine, 1-Dodecyl azacycloheptan-2-one (azone or laurocapram), N-Dodecyl diethanolamine, N-Dodecyl-hexahydro-2-thio-1H-azepine, N-Dodecyl-N-(2-methoxyethyl)acetamide, N-Dodecyl-N-(2-

methoxyethyl) isobutyramide, N-Dodecyl-piperidine-2-thione, N-Dodecyl-2-piperidinone, N-Dodecyl pyrrolidine-3,5-dione, N-Dodecyl pyrrolidine-2-thione, N-Dodecyl-2-pyrrolidone, 1-Farnesylazacycloheptan-2-one, 1-Farnesylazacyclopentan-2-one, 1-Geranyl azacycloheptan-2-one, 1, Geranylazacyclopentan-2-one, Hexahydro-2-oxo-azepine-1-acetic acid esters, N-(2, Hydroxyethyl)-2-pyrrolidone, 1-Laurylazacycloheptane, 2-(1-Nonyl)-1,3-dioxolane, 1-N-Octylazacyclopentan-2-one, N-(1-Oxododecyl)-hexahydro-1H-azepine, N-(1, Oxododecyl)-morpholines, 1-Oxohydrocarbyl-substituted azacyclohexanes, N-(1-Oxotetradecyl)-hexahydro-2-oxo-1H-azepine, N-(1 Thiododecyl)- morpholines, Acetamide and derivatives, Acetone, n-Alkanes (chain length between 7 and 16), Alkanols, diols, short-chain fatty acids, Cyclohexyl-1,1-dimethylethanol, Dimethyl acetamide, Dimethyl formamide, Ethanol, Ethanol/d-limonene combination, 2-Ethyl-1,3-hexanediol, Ethoxydiglycol (transcutol), Glycerol, Glycols , Lauryl chloride , Limonene , N-Methylformamide, 2-Phenylethanol, 3-Phenyl-1-propanol, 3-Phenyl-2-propen-1-ol, Polyethylene glycol, Polyoxyethylene sorbitan monoesters, Polypropylene glycol 425, Primary alcohols (tridecanol), Procter & Gamble system: small polar solvent (1,2-propane diol, butanediol, C3-6 triols or their mixtures and a polar lipid compound selected form C16 or C18 monounsaturated alcohol, C16 or C18 branched saturated alcohol and their mixtures), Span 20, Squalene, Triacetin, Trichloroethanol, Trifluoroethanol, Trimethylene glycol, Xylene, DMSO, Aliphatic alcohols, Decanol, Lauryl alcohol (dodecanol), Linolenyl alcohol, Nerolidol, 1-Nonanol, n-Octanol, Oleyl alcohol, Butyl acetate, Cetyl lactate, Decyl N,N-dimethylamino acetate, Decyl N,N-dimethylamino isopropionate, Diethyleneglycol oleate, Diethyl sebacate, Diethyl succinate, Diisopropyl sebacate, Dodecyl N,N-dimethylamino acetate Dodecyl (N,N-dimethylamino)-butyrate, Dodecyl N,N-dimethylamino isopropionate, Dodecyl 2-(dimethylamino)propionate, EO-5-oleyl ester, Ethyl acetate, Ethylaceto acetate, Ethyl propionate, Glycerol monoethers, Glycerol monolaurate, Glycerol monooleate, Glycerol monolinoleate, Isopropyl isostearate, Isopropyl linoleate, Isopropyl myristate, Isopropyl myristate/fatty acid monoglyceride combination, Isopropyl myristate/ethanol/L-lactic acid (87:10:3) combination, Isopropyl

palmitate, Methyl acetate, Methyl caprate, Methyl laurate, Methyl propionate, Methyl valerate, 1-Monocaproyl glycerol, Monoglycerides (medium chain length), Nicotinic esters (benzyl), Octyl acetate, Octyl N,N-dimethylamino acetate, Oleyl oleate, n-Pentyl N-acetylprolinate, Propylene glycol monolaurate, Sorbitan dilaurate, Sorbitan dioleate, Sorbitan monolaurate, Sorbitan monooleates, Sorbitan trilaurate, Sorbitan trioleate, Sucrose coconut fatty ester mixtures, Sucrose monolaurate, Sucrose monooleate, Tetradecyl N,N-dimethylamino acetate, Alkanoic acids, Capric acid, Diacid, Ethyloctadecanoic acid, Hexanoic acid, Lactic acid, Lauric acid, Linoelaidic acid, Linoleic acid, Linolenic acid, Neodecanoic acid, Oleic acid, Palmitic acid, Pelargonic acid, Propionic acid, Vaccenic acid, a-Monoglyceryl ether, EO-2-oleyl ether, EO-5-oleyl ether, EO-10-oleyl ether, Ether derivatives of polyglycerols and alcohols (1-O-dodecyl-3-O-methyl-2-0-(29, 39-dihydroxypropyl)glycerol), L-α-amino-acids, Lecithin, Phospholipids, Saponin/phospholipids, Sodium deoxycholate, Sodium taurocholate, Sodium tauroglycocholate (285), Aliphatic thiols, Alkyl N,N-dialkyl-substituted amino acetates, Anise oil, Anticholinergic agent pretreatment, Ascaridole, Biphasic group derivatives, Bisabolol, Cardamom oil, 1-Carvone, Chenopodium (70% ascaridole), Chenopodium oil, 1,8 Cineole (eucalyptol), Cod liver oil (fatty acid extract), 4-Decyloxazolidin-2-one, Dicyclohexylmethylamine oxide, Diethyl hexadecylphosphonate, Diethyl hexadecylphosphoramidate, N,N-Dimethyl dodecylamine-N-oxide, 4, 4-Dimethyl-2-undecyl-2-oxazoline, N-Dodecanoyl-L-amino acid methyl esters, 1,3-Dioxacycloalkanes, (SEPAs), Dithiothreitol, Eucalyptol (cineole), Eucalyptus oil, Eugenol, Herbal extracts, Lactam N-acetic acid esters, N-Hydroxyethalaceamide, 2-Hydroxy-3-oleoyloxy-1-pyroglutamyloxypropane, Menthol, Menthone, Morpholine derivatives, N-Oxide, Nerolidol, Octyl-b-D-(thio)glucopyranosides, Oxazolidinones, Piperazine derivatives, Polar lipids, Polydimethylsiloxanes, Poly [2-(methylsulfinyl)ethyl acrylate], Polyrotaxanes, Polyvinylbenzyldimethylalkylammonium chloride, Poly(N-vinyl-N-methyl acetamide), Prodrugs, Saline, Sodium pyroglutaminate, Terpenes and azacyclo ring compounds, Vitamin E (α-tocopherol), Ylang-ylang oil, N-Cyclohexyl-2-pyrrolidone, 1-Butyl-3-dodecyl-2-pyrrolidone, 1,3-Dimethyl-2-imidazolikinone, 1,5 Dimethyl-2-pyrrolidone, 4,4-Dimethyl-2-undecyl-2-

oxazoline, 1-Ethyl-2-pyrrolidone, 1-Hexyl-4-methyloxycarbonyl-2-pyrrolidone, 1-Hexyl-2-pyrrolidone, 1-(2 Hydroxyethyl)pyrrolidinone, 3-Hydroxy-N-methyl-2-pyrrolidinone, 1-Isopropyl-2-undecyl-2-imidazoline, 1-Lauryl-4-methyloxycarbonyl-2-pyrrolidone, N-Methyl-2-pyrrolidone,Poly(N-vinylpyrrolidone), Pyroglutamic acid esters, Acid phosphatase, Calonase, Orgelase, Papain, Phospholipase A-2, Phospholipase C, and Triacylglycerol hydrolase.

14. The method of claim 1 wherein the step of measuring the abilities of samples to increase the permeability of a test membrane is accomplished by making a plurality of electrical conductivity measurements and the step of analyzing the measurements is assisted by considering synergy values between chemical penetration enhancers in said samples.

15. The method of claim 1 wherein at least one of the selected compositions contains a pair of chemical penetration enhancers with a synergy value of 2 or more.

16. The method of claim 1 wherein at least one of the selected compositions contains a pair of chemical penetration enhancers with a synergy values of 4 or more.

17. The method of claim 1 wherein the step of analyzing the measurements is assisted by considering one or more potency phase maps.

18. The method of claim 1 wherein the step of analyzing the measurements is assisted by considering synergy values between one or more pairs of chemical penetration enhancers in the samples.

19. The method of claim 1 including the step of determining the irritation potential of the selected compositions whereby to identify one or more compositions having potent ability to increase the permeability of a body surface and low irritation potential.

20. The method of claim 19 in which the determination of irritation potential is accomplished with an *in vitro* measurement.

21. The method of claim 19 in which the determination of irritation potential is accomplished with an *in vivo* measurement.

22. The method of claim 19 in which the determination of irritation potential is accomplished using an interleukin-1α assay.

23. The method of claim 19 in which the determination of irritation potential is accomplished using a methyl thiazol tetrazolium assay.

24. The method of claim 19 in which irritation potential is measured using a 21-day cumulative irritation test.

25. The method of claim 19 including the step of combining each identified composition with a selected active component to form one or more candidate active component formulations.

26. The method of claim 25 including the step of testing each candidate active component formulation for the penetration of the active component into or through skin or mucosa.

27. The method of claim 26 in which the candidate active component formulation is placed on porcine or human skin and penetration of the active component through the skin is measured after a suitable incubation time.

28. The method of claim 27 in which penetration of the active component through the skin is measured using a Franz diffusion cell.

29. The method of claim 26 including the step of determining whether the tested candidate active component formulation can deliver the necessary active component amount through the skin.

30. The method of claim 29 in which the capacity of the tested candidate active component formulation to deliver the necessary active component amount through the skin is determined by comparing penetration of the candidate active component formulation with published data.

31. The method of claim 25 wherein the active component is a drug and further including the step of conducting animal testing to confirm the ability of an active component formulation to deliver sufficient drug across the skin to achieve therapeutic levels of the drug in the blood of animals.

32. The method of claim 31 in which the animal testing comprises *in vivo* experiments on hairless rats performed using leuprolide acetate as a model active component.

33. A composition identified by the method of claim 19 having potent ability to increase the permeability of skin and pharmaceutically acceptable irritation potential.

34. A method for identifying active component formulations comprising a plurality of chemical penetration enhancers having potent ability to increase the permeability of a body surface and low irritation potential, comprising:

(a) providing a library, said library comprising a plurality of samples comprising at least two chemical penetration enhancers;

(b) screening the library with a high throughput device by a method comprising (i) securing mammalian skin or mucosa to a device comprising a donor plate, the donor plate including a plurality of donor holes passing through the donor plate, (ii) introducing said samples into the donor holes, and (iii) measuring the abilities of the samples to increase the permeability of said mammalian skin or mucosa by making a plurality of electrical conductivity measurements;

(c) analyzing said electrical conductivity measurements to select compositions having high synergy values and potent ability to increase the permeability of said body surface;

(d) determining the irritation potential of the selected compositions whereby to identify one or more compositions having potent ability to increase the permeability of a body surface and low irritation potential;

(e) combining the identified compositions with a selected active component to form one or more candidate active component formulations;

(f) testing the candidate active component formulations for penetration of said

active component through a body surface;

(g) analyzing the results of the tests of penetration of said active component through said body surface to select an active component formulation having potent ability to increase the permeability of said body surface and low irritation potential.

35. An active component formulation with potent ability to increase the permeability of a body surface and low irritation potential selected according to the method of claim 34.

36. A formulation comprising a first and second chemical penetration enhancer having a 24-hour synergy value of 2 or more.

37. The combination of chemical penetration enhancers of claim 36 in which the synergy value is calculated according to the following equation

$$S = \frac{ER_{A+B}(X,Y)}{X.ER_A(Y) + (1-X).ER_B(Y)},$$

where $ER_{A+B}(X,Y)$ is the 24-hour enhancement ratio obtained with said formulation, A stands for said first chemical penetration enhancer, B stands for said second penetration enhancer, Y stands for the combined total concentration of said first and second chemical penetration enhancer in said formulation measured in weight/volume, X stands for the weight fraction said first chemical penetration enhancer in the formulation divided by Y, and $ER_A(Y)$ and $ER_B(Y)$ are the 24-hour enhancement ratios obtained with a second and third formulation where the chemical penetration enhancers A and B are replaced in said formulation with pure components A and B, respectively, each at concentration Y weight/volume.

38. The formulation of claim 36 in which the 24-hour synergy value is 4 or more.

39. A formulation comprising a first and second chemical penetration enhancer with potent ability to increase the permeability of skin showing sufficient partitioning

of components of said formulation between the stratum corneum of skin and other layers of skin to exhibit low irritation potential.

40. The formulation of claim 39 wherein the 21-day cumulative irritation test score of said formulation is less than about 199.

41. A composition comprising a first and second chemical penetration enhancer having potent ability to increase the permeability of skin and low irritation potential to enable transdermal delivery of a drug having a molecular weight of at least 500 Da with pharmaceutically acceptable irritation potential.

42. A composition comprising sodium laurel ether sulfate and 1-phenyl piperazine having potent ability to increase the permeability of skin and low irritation potential.

43. A composition comprising N-lauryl sarcosine and sorbitan monolaurate having potent ability to increase the permeability of skin and low irritation potential.

44. A formulation for topical and/or transdermal administration of a drug, comprising:

(a) a therapeutically effective amount of said drug;

(b) a pharmaceutically acceptable vehicle suitable for topical or transdermal drug administration;

(c) a first and second chemical penetration enhancer, the synergy value between said first and second chemical penetration enhancer being at least about 2;

wherein said formulation has a pharmaceutically acceptable irritation potential and the skin conductivity enhancement ratio of the formulation is at least about 30.

45. A composition comprising a first and second chemical penetration enhancer wherein the 24-hour synergy value between said first and second chemical penetration enhancer is at least about 2 and wherein the irritation antergy factor between said first and second chemical penetration enhancer is at least about 2,

said irritation antergy factor being computed using the MTT 4-hour cell viability percentage measure of irritation potential.

46. The formulation of claim 44 wherein said chemical penetration enhancers are selected from the group consisting of surfactants, azone and related compounds, solvents and related compounds, fatty alcohols, fatty esters and fatty acids.

47. A method for treating a disease that is responsive to administration of a drug comprising applying the formulation of claim 44 to a patient's body surface.

48. A system for topical or transdermal administration of a drug, comprising:
(a) the formulation of claim 44;
(b) at least one drug reservoir, said reservoir containing said formulation;
(c) means for securing said system to a body surface.

49. A transdermal patch comprising the formulation of claim 44.

50. A method for delivering an active component, comprising applying a formulation to the skin of a mammal said formulation comprising:
(a) an effective amount of said active component;
(b) a cosmetically or pharmaceutically acceptable vehicle;
(c) a first chemical penetration enhancer; and
(d) a second chemical penetration enhancer;
wherein said formulation has an irritation potential that is less than that of 1.5%wt/vol oleic acid in a vehicle consisting of phosphate buffered saline, the 24-hour synergy value between the first and second chemical penetration enhancer is at least about 2, and the 24-hour conductivity enhancement ratio of said formulation measured with porcine skin is at least about 30.

51. A method for screening for formulations providing potent ability to increase the permeability of skin and low irritation potential, comprising:
(a) providing a library of samples, a plurality of said samples comprising at least two chemical penetration enhancers;
(b) using a high throughput device to assay the abilities of said samples to

permeabilize skin;

(c) analyzing the results of the assay to identify the presence hot spots or suspected hot spots to select one or more compositions for irritation potential measurement; and

(e) measuring the irritation potential of the selected compositions;

whereby formulations providing potent ability to increase the permeability of skin and low irritation potential may be efficiently discovered.

52. A method for making a formulation providing potent ability to deliver an active component and low irritation potential, comprising:

(a) providing at least two materials wherein in aggregate the components of said at least two materials comprise a first and second chemical penetration enhancer, an active component and a vehicle;

(b) combining said at least two materials in a predetermined ratio;

whereby a formulation is made, said formulation having a 24-hour porcine skin conductivity enhancement ratio of at least about 30 and an MTT 4-hour cell viability percentage of less than about 15%.